Review Article

Imaging of coronary atherosclerosis in various susceptible groups

Ravi Kiran Munnur, Nitesh Nerlekar, Dennis T. L. Wong

Monash Cardiovascular Research Centre/MonashHEART, Clayton, Victoria, Australia

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Correspondence to: Ravi Kiran Munnur. Monash Cardiovascular Research Centre/Monash Heart, Clayton, Victoria, Australia.
Email: kiran.munnur@gmail.com.

Abstract: Coronary artery disease (CAD) is the leading cause of death and disability worldwide. Atherosclerosis, which is the primary pathophysiologic mechanism for the development of plaque leading to CAD, is a multifactorial process resulting from a complex interplay between genetic susceptibility and various risk factors such as hypertension (HT), dyslipidaemia, diabetes mellitus (DM) and smoking. In addition, influences from other disease states such as chronic kidney disease (CKD), obesity and the metabolic syndrome as well as gender and ethnic diversity also contribute to the disease process. Insights from pathological observations and advances in cellular and molecular biology have helped us understand the process of plaque formation, progression and rupture leading to events. Several intravascular imaging techniques such as intravascular ultrasound (IVUS), Virtual histology IVUS (VH-IVUS) and optical coherence tomography (OCT) allow *in vivo* assessment of plaque burden, plaque morphology and response to therapy. In addition, non invasive assessment using coronary artery calcium (CAC) score allows risk stratification and plaque burden assessment whilst computed tomography coronary angiography (CTCA) allows evaluation of luminal stenosis, plaque characterisation and quantification. This review aims to summarise the results of invasive and non-invasive imaging studies of coronary atherosclerosis seen in various high-risk populations including DM, metabolic syndrome, obesity, CKD and, gender differences and ethnicity. Understanding the phenotype of plaques in various susceptible groups may allow potential development of personalised therapies.

Keywords: Coronary artery disease (CAD); atherosclerosis; intravascular ultrasound (IVUS); optical coherence tomography (OCT); computed tomography coronary angiography (CTCA); coronary artery calcium score

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Introduction

Coronary artery disease (CAD) is the leading cause of death and disability worldwide (1,2). Atherosclerosis, which is the primary pathophysiologic mechanism for the development of plaque leading to CAD, is a multifactorial process resulting from a complex interplay between genetic susceptibility and various risk factors such as hypertension (HT), dyslipidaemia, diabetes mellitus (DM) and smoking (3). In addition, influences from other disease states such as chronic kidney disease (CKD), obesity and the metabolic syndrome as well as gender and ethnic diversity also contribute to the disease process. Insights from pathological observations and advances in cellular and molecular biology have helped us understand the process of plaque formation, progression and rupture leading to events. Several intravascular imaging techniques such as intravascular ultrasound (IVUS), radiofrequency IVUS (RF-IVUS) or virtual histology IVUS and optical coherence tomography (OCT) allow *in vivo* assessment of plaque burden, plaque morphology and response to therapy. In addition, non invasive assessment using coronary artery calcium (CAC)

score allows risk stratification and plaque burden assessment whilst computed tomography coronary angiography (CTCA) allows evaluation of luminal stenosis, plaque characterisation and quantification.

This review aims to summarise the results of invasive and non-invasive imaging studies of coronary atherosclerosis seen in various high-risk populations including DM, HT, metabolic syndrome, obesity, CKD and, gender differences and ethnicity. Understanding the phenotype of plaques in various susceptible groups may allow potential development of personalised therapies.

Background: atherosclerosis—pathophysiology

Atherosclerosis is a result of deranged lipids, inflammation and endothelial dysfunction (4). Dyslipidemia is the most important risk factor in the pathogenesis of atherosclerosis, which is evident in patients with genetic hyperlipidemia who have increased incidence of CAD even in the absence of other risk factors. Conversely, lower levels of lipids are sufficient to cause atherosclerosis in the presence of other cardiovascular risk factors. The mechanism of this interaction and the role of individual cardiovascular risk factors in the pathogenesis of atherosclerosis are not well understood. Atherosclerotic plaques have a predilection to develop in regions of an artery with low or oscillatory endothelial shear stress. Binding of low density lipoprotein-cholesterol (LDL-C) to intimal proteoglycans is an important initial step (5) followed by LDL modification by oxidation and aggregation resulting in foam cells (6). This leads to endothelial dysfunction, smooth muscle cell migration and stimulation of innate and adaptive immune responses. Higher levels of LDLs are required to initiate the disease than to sustain the lesions once they have formed (7,8). Foam cells, macrophages and smooth muscle cells undergo apoptosis, and along with intraplaque haemorrhage lead to formation of necrotic core. The lesion is then described as a fibroatheroma. Smooth muscles cells undergo modulation and migration, and are a source of fibrous cap made of type I collagen that replaces the arterial intima and separates the necrotic core from the lumen (9). Some plaques undergo fibrosis whilst in some, apoptotic cells, extracellular matrix and necrotic core material act as nidus for microscopic calcium granules which can expand subsequently to forms plates or large lumps of calcium deposits (10). During atherogenesis, the vessel segment undergoes positive remodelling, expanding outward in such a way that the lumen is not compromised. This is often seen in fibroatheromas and is positively correlated to the size of necrotic core and inflammation (11,12). Constrictive remodelling is seen in plaques that are rich in fibrous tissue (12). The development of atherosclerosis may lead to either obstruction of lumen limiting blood flow or may lead to acute coronary syndrome (ACS) due to plaque rupture, and less often due to plaque erosion and calcified nodule.

Diabetes mellitus (DM)

DM is a growing epidemic worldwide and is highly atherogenic with contributing factors being hyperglycaemia, advanced glycation end products along with inflammation and oxidative stress (13). Amongst the traditional cardiovascular risk factors, it is the strongest predictor of future myocardial infarction, and is associated with significantly higher mortality as well as poorer outcome after percutaneous coronary intervention when compared to non-diabetic counterparts (14-16). Necropsy studies have suggested that DM is associated with a greater and more diffuse disease burden particularly in the distal vessels (17) and numerous imaging studies have allowed us to understand the disease *in vivo*.

In a systematic analysis of 2,237 subjects from randomised controlled studies evaluating plaque progression in response to various pharmacological therapies using serial IVUS, the extent of coronary atherosclerosis, pattern of arterial remodelling and disease progression was compared between DM and non-DM patients. It was observed that DM subjects had more extensive atherosclerosis and total atheroma volume (TAV) when compared to non-DM subjects (199.4±7.9 *vs.* 189.4±7.1 mm^3, P=0.03). Despite the presence of more extensive disease, DM subjects had smaller lumen and similar external elastic membrane (EEM) accounting for greater percent atheroma volume (PAV) [(40.2±0.9)% *vs.* (37.5±0.8)%, P<0.0001]. It was also observed that insulin-requiring diabetics had even smaller EEM and lumen volumes resulting in even larger PAV. Although the prevalence of HT and dyslipidaemia was higher in DM group, DM was an independent predictor of increased plaque burden. Surprisingly, in this systematic analysis the number of segments affected was not different in DM and non-DM subjects raising the possibility that DM could lead to a more aggressive localised disease and not necessarily a generalised disease as previously thought. DM patients were more likely to have plaque PAV progression and were less likely to undergo plaque regression despite the use of established medical therapies (18).

Plaque regression rates achieved with an intensive lowering regimen of low-density lipoprotein cholesterol (LDL-C) in DM, achieves the same regression rates as non-DM subjects with non-intensive lowering regimens. Of note, the achieved LDL-C level in this pooled study was 80 mg/dL. However, target LDL levels of 61 mg/dL were achieved in the SATURN trial, where the response rate to high intensity statin therapy demonstrated equivalent degrees of PAV and TAV regression in DM and non-DM subjects when an LDL-C <70 mg/dL was achieved (19). Although there was comparable TAV regression in both groups when post-therapy LDL-C was >70 mg/dL, PAV regression was greater in the non-DM group [(–1.01±0.21)% *vs.* (–0.31±0.23)%, P=0.03]. These observations suggest that abnormalities of arterial remodelling also influence the clinical expression of atherosclerotic disease in DM.

To examine the natural history of vascular remodelling and predictors of vessel shrinkage, 237 DM patients were examined using IVUS (20). Significant lumen shrinkage was associated with vessel shrinkage and was identified in 37.1% of segments. Independent predictors were insulin requirement, glycated haemoglobin, Apolipoprotein B, HT, the number of diseased vessels and prior revascularisation. It was observed in another study that even at angiographically normal sites, mild atherosclerosis was detected by IVUS in both DM and non-DM patients. Despite both the groups having similar plaque area (34.5% *vs.* 31.6%) vessel area and lumen area in diabetic patient were significantly smaller than in the non-diabetic patient (15.5 *vs.* 17.8 mm^2, P<0.01; and 10.1 *vs.* 12.2 mm^2, P<0.01 respectively), again suggesting a constrictive mechanism even in early stages of atherosclerosis (21). Furthermore, it has been noted that in pre-DM patients there is evidence of smaller coronary size and diffuse luminal narrowing particularly in the distal left anterior descending artery (22). The mechanisms that promote impaired arterial remodelling in diabetic subjects is not fully understood and it has been postulated that impaired endothelial-dependent relaxation (23), increased deposition of calcium (24) and fibrous tissue (25) deposition in arterial wall may limit vessel expansion from plaque accumulation. This is particularly more pronounced in insulin-treated patients leading to speculation that smooth muscle proliferation and fibrous tissue deposition in response to insulin may impair arterial wall expansion (26).

The use of RF-IVUS and OCT imaging has allowed us to determine plaque composition in addition to the assessment of plaque burden. In a study of stable angina pectoris patients, the percentage area of necrotic core and dense calcium on IVUS was found to be significantly higher in DM group compared to non-DM group. It was also observed that the frequency of RF-IVUS derived thin cap fibro-atheroma (TCFA) and fibro calcific plaques were higher in DM group (27). Although the incidence of ruptured plaques and TCFA at culprit lesion sites were similar, non-culprit lesion (NCL), TCFA were observed more frequently in DM patients than in non-DM patients, in a three-vessel OCT study of patients presenting with ACS (28). DM patients demonstrate a larger lipid index (LI = averaged lipid arc × lipid length): 1,164±716 and 1,086±693 *vs.* 796±417 mm; P<0.001 and higher prevalence of calcification and thrombus, and those with HbA1C of ≥8% have larger LI and the highest prevalence of TCFA and macrophage infiltration (29). In another OCT study, DM subjects with higher insulin resistance were observed to have more frequent TCFA's with significantly thinner cap thickness compared to DM subjects with lower insulin resistance (30). These observations suggest that poorly controlled DM and insulin resistance is associated with high-risk plaque features.

Niccoli *et al*. evaluated angiographic and OCT parameters in DM and non-DM patients with an index ACS (31). Angiographically, although DM was associated with higher stenosis score and extent index, these patients surprisingly had more collateral vessels directed towards the culprit artery. On OCT examination, minimum lumen area (MLA) of the culprit segment was similar in both the groups. In DM patients, less lipid quadrants, smaller lipid arcs (2.3±1.3 *vs.* 3.0±1.2; P=0.03 and 198°±121° *vs.* 260°±118°; P=0.03), more frequent superficial calcified nodules (79% *vs.* 54%, P=0.04), greater number of calcified quadrants and a wider calcified arc (1.7±1.0 *vs.* 1.2±0.9; P=0.03 and 126°±95° *vs.* 81°±80°; P=0.03) were noted. Despite accelerated atherosclerosis seen in diabetic patients, they do not present early with ACS and it has been speculated that there may be an unknown protective mechanism that might delay the onset of a first event (32).

In a sub-analysis of the TRUTH study, the effect of statin therapy on plaque composition was studied in DM and non-DM groups using serial RF-IVUS (33). Although there was reduction in the fibro fatty component in both groups, the DM group had less reduction at follow up. In an IVUS study that examined the relationship between glycaemic status and CAD, fasting blood sugars, HbA1C and DM were associated with severity and progression of atherosclerosis (34). A similar observation was made in the COSMOS study, where despite similar improvements

in lipid levels, plaque regression was less pronounced in patients with high HbA1C.

DM is often associated with HT and dyslipidaemia and it is not surprising that greatest clinical benefit of medical management in diabetes is seen with optimisation of blood pressure (BP) (35) and lipids (36). In an IVUS study, disease progression was compared in patients who were stratified according to the achievement of treatment goals of individual risk factors: HbA1C<7%, LDL-C <2.5 mmol/L, Triglycerides <1.7 mmol/L, systolic blood pressure (SBP) <130 mmHg, high sensitivity C-reactive protein (hsCRP) <2 mg/L. It was observed that slowing of progression of PAV correlated with the greater number of risk factors that achieved treatment goals (37).

DM is a significant CV risk factor that causes accelerated coronary atherosclerosis, vessel shrinkage and increased events. It is further complicated by attenuated plaque regression in response to conventional treatment modalities. Optimisation of all other associated risk factors apart from intense management of sugars and lipids appears to be the best strategy.

Metabolic syndrome

Metabolic syndrome as defined by National Cholesterol Education Program Adult Treatment Panel III criteria (38) consists of ≥3 of the following criteria: body mass index (BMI) ≥30kg/m^2, triglyceride level ≥150 mg/dL, HDL-C (<40 mg/dL in men and, <50 mg/dL in women), impaired fasting glucose (100 to 125 mg/dL), and high systolic or diastolic blood pressure (≥130 mmHg or ≥85mmHg respectively). It is not clearly understood if the metabolic syndrome is truly a syndrome or just a cluster of risk factors. Although the metabolic syndrome is associated with higher clinical events, it has been suggested that the risk is equal to the sum of individual risk factors (39).

The extent and progression of atherosclerosis was compared between DM, metabolic syndrome and those with neither diagnosis from data pooled from seven clinical trials involving 3,459 patients who were studied with serial IVUS (40). DM, when compared to MS and neither diagnosis, was associated with greater PAV [(40.3±9.0)%, (37.6±8.9)%, and (38.1±9.1)%, P<0.001] , greater lumen constriction (290.6±111.7 *vs.* 298.1±105.5 mm^3, P<0.0001) and greater plaque progression [(+0.8±0.3)%, (+0.3±0.2)%, and (+0.1±0.2)%, P<0.0001]. Despite the metabolic syndrome group having the most risk factors, the extent of atherosclerosis and progression rate was no greater than those with neither diagnosis. Another observation was that EEM and lumen were larger in metabolic syndrome group compared to neither diagnosis (501.3±174.3 *vs.* 484.4±160.7 mm^3), for the same amount of PAV and TAV. Interestingly, the IVUS findings in sole DM patients *vs.* DM patients with concomitant metabolic syndrome were no different. In a Korean study involving 2,869 symptomatic subjects who underwent CTCA, metabolic syndrome was independently associated with the presence and severity of CAD only in the non-DM group but not in the DM group (41). These observations highlight the significant risk of coronary atherosclerotic disease progression when metabolic syndrome leads to DM.

It has been observed that although metabolic syndrome was an independent predictor of plaque progression, when its individual components were used it was no longer significant. Whilst hypertriglyceridemia and BMI were independent predictors in one study (42), abdominal obesity and high BP were found to be significantly associated in another study where asymptomatic subjects were assessed using CTCA (43). The impact of metabolic syndrome and its components on coronary plaque progression in response to intensive statin therapy was studied in the JAPAN-ACS trial (44). Although percent change in PAV was no different between metabolic syndrome and non-metabolic syndrome group, in the former, response to therapy was attenuated with increasing number of metabolic syndrome components, especially ≥4 risk factors. In addition, it was observed that percent BMI change was an independent predictor of plaque regression. It has been demonstrated in another study that prognostic information is added to the diagnosis of metabolic syndrome if stratification is performed by hsCRP (45).

Although a previous RF-IVUS study showed a higher prevalence of TCFA in patients with DM and metabolic syndrome (46), no such association was seen in PROSPECT trial and other RF-IVUS studies (47,48). DM, metabolic syndrome and a control group were compared where OCT was used to characterize coronary plaque. It was observed that Lipid Index was higher in DM and metabolic syndrome group compared to those with neither diagnosis while calcification was more frequent in DM group. Of note, frequency of TCFA, macrophage accumulation and micro vessels did not differ among the three groups and ACS was the only independent predictor of TCFA (28). Yet in another study, when clinical predictors of culprit plaque rupture were assessed on IVUS in ACS patients who were divided into two groups based on the presence or

absence of plaque rupture (49), the prevalence of metabolic syndrome was higher in the plaque rupture group. The waist circumference in these patients was greater and they had lower HDL-C levels.

Metabolic syndrome as a syndrome or due to individual risk factor components appears to be associated with atherosclerotic disease progression. The presence of high-risk plaque features such as high lipid content and positive remodelling, and the association of metabolic syndrome with plaque rupture suggests that this is a high-risk group. In addition, as metabolic syndrome is regarded as a prediabetic state (50), aggressive risk factor management, especially central adiposity, is essential to prevent cardiovascular disease progression from the development of frank DM.

Gender

IVUS analysis has demonstrated that woman have less extent of CAD compared to men, which has also been confirmed by pathologic studies (51-54). It has also been proposed that women take longer to develop significant atherosclerosis, which may relate to differences in the influence of risk factors between the sexes. It has been hypothesised that oestrogen has an anti-inflammatory effect that might stabilise existing plaque and slow plaque progression with postmenopausal women (>65 years) having the same risk of CAD as men. However, oestrogen has shown no protective effect against plaque erosion which is more common in women (55).

In patients presenting with ACS, no significant sex difference was seen in culprit plaque characteristics as determined by OCT and IVUS (56,57). In a follow-up RF-IVUS analysis of culprit lesions in ACS patients (58), it was noted that women had a greater prevalence of TCFA (62% *vs.* 52%, P=0.078) compared with men. However, women were also more likely to be diabetic and have higher hsCRP levels, which when adjusted for on multivariate analysis, negated the differences seen in the presence of TCFA.

In the PROSPECT study, it was demonstrated that majority of future MACE arose from plaques that caused only mild stenosis angiographically (diameter stenosis <50%) but were characterised by high risk plaque features such as large plaque burden ≥70%, small MLA ≤4 mm^2, and/or are TCFA's as assessed by RF-IVUS (59). A sex-based analysis of patients from the PROSPECT trial revealed that women had fewer vessels with NCL and more focal NCL, with, less calcium, necrotic core and fibrous volume. Whilst women were more likely to have at least one high risk plaque feature, the attributable risk of MACE appears to be highly associated with TCFA in women and PB >70% in men. Despite these differences, the NCL MACE between men and women at three years was similar (6.1% *vs.* 7.5%, P=0.49) (60). The authors postulate that these observed differences in NCL plaque characteristics might balance out to explain the similar event rates. It is important to note that most of these sex differences are usually seen in patients <65 years of age and that plaque characteristics become increasingly similar between men and women with increasing age (56).

In a meta-analysis of 170,000 participants on statin therapy, women demonstrated the greatest proportional benefit in terms of reduction of plaque and MACE events (61), however the factors that contribute to these effects are poorly understood. In the SATURN trial of intensive lipid-lowering therapy (62), female sex was independently associated with coronary atheroma plaque regression to statin treatment. Women achieved greater PAV reduction only if LDL-C levels reached ≤70 mg/dL despite fewer women reaching target levels compared to men and it was suggested that women may derive greater benefit from rosuvastatin compared to atorvastatin. Interestingly, plaque regression was more likely to occur in women with DM, stable angina pectoris, and higher baseline LDL-C and CRP levels. The reduction was irrespective of HDL-C levels, which is in contrast to the findings in the REVERSAL trial where HDL-C levels above the collective mean were significantly associated with plaque regression (63). Of note, it was observed that on treatment CRP levels and not the absolute LDL-C change was shown to be associated with plaque reduction and MACE in a sub study of SATURN (64).

These findings highlight the complex interaction between female sex, cardiovascular risk factors, CRP and HDL-C and their association with plaque regression, response to therapy and events.

Ethnicity

Differences in atherosclerotic disease patterns have been identified in various ethnic groups. It is not well understood as to whether this is attributable to genetic differences or due to the differences in prevalent risk factors. In seven clinical trials that utilized serial IVUS, African American patients were compared to Caucasians, and were more likely to be female with a greater number of co-morbidities. Despite a higher use of anti-atherosclerotic therapies, African American

patients had higher LDL-C, CRP and SBP at baseline and follow up. Although baseline atheroma volume did not differ, at follow up there was greater atheroma progression in the African American group (0.51±2.1 *vs.* −3.1±1.7 mm^3, P=0.01), despite adjusting for the differences in risk factor control (0.1±2.1 *vs.* −3.7±1.7 mm^3, P=0.02) (65).

Ethnic differences were assessed in an IVUS comparison of left main artery disease between white and Asian patients (Japanese and South Korean) with matching parameters of age, gender and prevalence of DM. Asian patients had lower BMI and lipid levels, and were observed to have smaller lumen (5.2±1.8 *vs.* 6.2±14 mm^2; P<0.0001), larger vessel area (20.0±4.9 *vs.* 18.4±4.4 mm^2; P<0.0001) and larger plaque burden [(72±10)% *vs.* (64±12)%; P<0.0001)], while white patients had greater calcification despite having less plaque volume (66). On the contrary, when coronary angiography was used to compare coronary lesions between Mainland Chinese and Australians, the incidence of left main artery and left anterior descending artery lesions in Australians were higher than that for Chinese of the same gender. It was observed that Australians typically have artery lesions ten years earlier (67).

South Asians from Mediator of Atherosclerosis in South Asians living in America (MASALA) study were compared to the ethnic groups in Multi-Ethnic Study of Atherosclerosis (MESA) consisting of whites, African Americans, Latinos and Chinese (68). CAC score was used for comparison and it was observed that South Asian men had similar CAC burden as white men but higher scores than other ethnic groups. South Asian women ≥70 years were found to have higher CAC than most other groups. Additionally, in a study that used CTCA and CAC to compare symptomatic South Asians and Caucasians with similar risk factors, it was observed that in patients aged ≥50 years, South Asians had a greater mean number of arterial segments with both obstructive and non obstructive plaque, and higher CAC scores. Interestingly, in patients ≤50 years, Caucasians showed a higher mean number of diseased segments with non obstructive plaques with similar CAC scores suggesting that Caucasians are likely to have more diffuse atherosclerosis at an earlier age although South Asians had higher prevalence and severity of disease (69).

In a quantitative coronary angiography study, symptomatic South Asians were observed to have a higher percentage multivessel disease, higher mean percent stenosis per vessel and smaller proximal LAD luminal diameters when compared to Caucasians (70). These findings are important as South Asians form 20% of the world's population and are among the fastest growing ethnic groups in various countries. It is estimated that by 2020, South Asians will contribute to 40% of the global cardiovascular burden (71).

These observations highlight the differences in coronary plaque burden and prevalence that is seen in various ethnic groups. The effects of ethnicity may contribute to cardiovascular disease burden beyond traditional risk factors and further studies are needed to confirm these findings.

Hypertension (HT)

HT is defined as BP >140/90 mmHg. It is an extremely common disease affecting over a billion people worldwide and World health organisation has reported that suboptimal BP is the no. 1 attributable risk of death throughout the world. CAD is a common target organ damage noted (72) and SBP appears more strongly associated with coronary events than DBP (73) Uncertainty exists regarding the optimal use of anti hypertensive drugs in patients with CAD. Although guidelines recommend lower BP goals for patients with CKD and diabetes, the target BP levels in patients with CAD is not different from recommendations for the general population.

Aggressive BP control appears to be beneficial in patients with CAD with reduction in clinical events and anti hypertensive medications may have anti atherosclerotic effects. In the CAMELOT study, the effect of Amlodipine, Enalapril and placebo on CV events in patients with CAD and normal BP was studied. Baseline BP averaged 129/78 mmHg for all patients. Cardiovascular events occurred in 151 (23.1%) placebo-treated patients, in 110 (16.6%) amlodipine-treated patients [hazard ratio (HR), 0.69; 95% CI, 0.54–0.88 (P=0.003)], and in 136 (20.2%) enalapril-treated patients (HR, 0.85; 95% CI, 0.67–1.07 (P=0.16)]. In the IVUS substudy, there was significantly less progression of atherosclerosis in the ambodipine group *vs.* placebo group, when SBP was greater than the mean (P=0.02) (74). Similar observation was made with azelnedipine, another di-hydropyridine calcium channel blocker in a separate study (75). In a substudy of CAMELOT, the progression of coronary atherosclerosis was compared between patients with, normal BP, "pre-hypertensive" BP and hypertensive BP. In patients with "hypertensive" BP, there was an increase in atheroma volume [12.0±3.6 mm^3 (least square mean ± SE)]. In comparison, those with "pre-hypertensive" BP had no major change (0.9±1.8 mm^3) and those with "normal" BP had a decrease of 4.6±2.6 mm^3 (P<0.001 by analysis of covariance; P<0.05 for comparison

of all pairs) (76). In a post hoc, pooled analysis of individual patient data from four IVUS trials, it was observed that atheroma volume statistically significantly decreased at follow-up IVUS in patients who received beta-blockers (P<0.001) and did not change in patients who did not receive beta-blockers (P=0.86). The obvious limitation of this study is that patients were not randomly assigned to beta blocker therapy and other interventions could have influenced the results (77).

The beneficial effect of statins in plaque progression has been studied in various IVUS trials. There may be an attenuated response to statins due to the presence of other CV risk factors and this complex interplay is not fully understood. Nozue *et al*. evaluated the impact of DM and HT on coronary atherosclerosis during statin therapy using RF-IVUS. Frequency of progression in atheroma volume was studied in patient groups of DM+HT+, DM+HT-, DM-HT+ and DM-HT- and was found to be 60%, 33%, 45% and 24% respectively, P=0.03. There was no difference in changes in plaque composition. This study highlights the significant impact of HT on response to statin therapy (78). In another study, the impact of LDL-C and SBP on coronary plaque progression was investigated. Slowest CAD progression was seen in the group with very low LDL-C and normal SBP, followed by very low LDL-C and SBP >120 and least benefit was seen in the group with LDL-C >70 mg/dL and normal SBP. In this study, lower levels of LDL-C had greater impact on progression of CAD than SBP. These studies highlight the need for intensive control of global risk in patients with CAD (79).

It has been speculated that some of the antihypertensive medications may exert anti atherosclerotic effect by anti-inflammatory action. Antiogensin receptor blockers (ARB) are suggested to have unique pleiotrophic effects in addition to renin angiotensin system inhibition. In a study that employed integrated backscatter IVUS, the effect of telmisartan on coronary plaque component and local inflammatory cytokines was assessed. Significant increases in fibrous volume [(51.2±10.4)% to (58.3±7.7)%, P=0.03] and reductions in lipid volume [(38.4±12.4)% to (32.8±9.7)%, P=0.03] were observed on IVUS in the telmisartan group, while there were no significant changes in the plaque component in the control group. Coronary sinus levels of inflammatory cytokines [matrix metalloproteinase (MMP)3, tumor necrosis factor-α, high-sensitivity C-reactive protein and MMP9] were lower after than before treatment in the only telmisartan group (7.7±6.1 to 5.5±4.9 ng/mL, 3.1±1.9 to 2.3±2.0 pg/mL, 5.6±6.0 to 2.2±2.4 mg/L, 36.1±39.3 to 19.9±27.5 ng/mL, P=0.02, P=0.03, P=0.04, P=0.07, respectively) (80). Furthermore, the impact of olmesartan on clinical outcomes and progression of atherosclerosis evaluated by IVUS in patients with stable angina pectoris patients was studied in OLIVUS–Ex trial. Cumulative event-free survival was significantly higher in the Olmesartan group than in the control group (P=0.04; log-rank test). Serial change in TAV [(0.6±12.9)% *vs*. (5.4±15.5)% P=0.016 and PAV (−0.7±13.6)% *vs*. (3.1±12.5)%, P=0.038 were significantly lower in the Olmesartan group than in the control group. Interestingly, no statistically significant correlation was observed between BP reduction and plaque progression rate (81).

HT is a major health problem and several studies have established the adverse cardiovascular outcomes due to HT. Hence, effective treatment of HT is necessary. Optimisation of BP assumes great importance in patients with CAD and there appears to be benefit in treating pre-HT. Anti hypertensive medications confer benefit by not only reducing BP but may also exert anti-atherosclerotic effects.

Chronic kidney disease (CKD)

Studies of coronary atherosclerosis in CKD patients are limited and heterogeneous. Studies differ significantly in methodology and patient inclusion with some dedicated to patients requiring renal replacement therapy (RRT), and others involving those with progressively declining glomerular filtration rate (GFR) not yet on dialysis. Therefore there is marked variation in results from these studies. What is of certainty however is that there is a very high prevalence of obstructive CAD in these patients (82) and the primary cause of death is due to cardiovascular events (83).

The pathophysiology of vascular disease in CKD patients differs to the general population (84). In addition to traditional risk factors, there is a complex and poorly understood interplay between malnutrition, inflammation, atherosclerosis and calcification that play a role in the development of vascular disease (83). Autopsy studies have confirmed that CKD patients have an extensive atherosclerotic burden. Schwarz *et al*. performed a post-mortem analysis of 27 end stage renal disease (ESRD) patients comparing epicardial artery plaque characteristics with age and sex matched normal renal function patients. The authors demonstrated that ESRD patients had a greater proportion of calcified plaques, greater media thickness

(187±53 *vs.* 135±29 μm in controls, P<0.05) and reduced lumen area (3.27±1.44 *vs.* 1.32±0.18 mm^2, P<0.05) with a trend to higher intima thickness (158±38 *vs.* 142±31 μm, P=ns) but no overall difference in plaque area (4.09±1.50 *vs.* 4.39±0.88 mm^2, P=ns) (83). Further pathologic analysis has confirmed this greater proportion of dense coronary calcific disease and media thickness, amongst all groups of renal dysfunction compared to normal controls, independent of other cardiovascular risk factors (85).

There is a limited literature with respect to non-invasive techniques; CACS has been widely investigated in patients with CKD with clear evidence of increasing CACS burden as GFR decreases (86,87). As calcification in ESRD tends to be within the media as described pathologically, this partly explains the probably reduced specificity for obstructive disease (88). CTCA is an ideal non-invasive tool for coronary luminal plaque assessment. However the large degree of coronary calcification may impact upon interpretation and the rates of unevaluable segments or patients' ranges from 10–27% (89-91). Despite this, the sensitivity and negative predictive value for obstructive disease remains high (93% and 97%) at the expense of reduced specificity and positive predictive value (63% and 41%) as was seen in a study of 138 CKD patients undergoing both CTA and invasive coronary angiogram (89). No CT study has yet imitated invasive studies to evaluate high-risk plaque features between normal, CKD and ESRD patients.

There have been several small *in vivo* analyses of coronary plaques to investigate the impact of renal function, predominantly with the use of IVUS. Several studies have demonstrated that plaque characteristics worsen significantly with declining GFR. Miyagi and colleagues evaluated two groups (GFR <60 and >60 mL/min) of patients undergoing percutaneous intervention (PCI) with IVUS guidance and found that impaired renal function related to a higher percentage of lipid volume and reduced percentage of fibrous volume [(36.7±10.6)% *vs.* (28.7±9.3)%, P<0.001 and (59.1±8.7)% *vs.* (66.3±8.3)%, P<0.001, respectively]; however there were no dialysis patients included in this analysis nor was calcific plaque assessed (92). A study of 136 ACS patients who underwent culprit artery angioscopy revealed a greater proportion of "yellow plaques" in CKD *vs.* non-CKD patients [4.0 (2.0 to 6.0) *vs.* 2.0 (1.0 to 4.0), P=0.001]. CKD was an independent predictor of multiple yellow plaques per vessel, conferring a three times greater risk on multivariate regression analysis (odds ratio 3.49; 95% confidence interval (CI): 1.10 to 11.10, P=0.03) (93). Furthermore, in a study of 310 ACS patients that had culprit artery IVUS interrogation, progressively declining GFR was an independent predictor of plaque rupture (odds ratio 0.979, 95% confidence interval 0.963 to 0.994, P=0.008), with patients in the lowest creatinine clearance group having a greater degree of lesion site plaque burden and plaque length (94).

In a substudy of the PROSPECT trial that included only ACS patients, CKD patients (n=73) compared to non-CKD (n=573) had a higher prevalence of necrotic core (15.0% *vs.* 13.0%, P=0.0001) and dense calcium (8.2% *vs.* 6.4%, P=0.0001), with low fibrous tissue (57.7% *vs.* 59.8%, P=0.0001) in non-culprit artery plaques (95). Similarly, an OCT study of non-culprit plaques in a group of patients by Kato *et al.* observed higher lipid index [mean lipid arc×lipid length 1,248.4±782.8 mm (non-CKD) versus 1,716.1±1,116.2 mm (CKD); P=0.003], higher calcium prevalence [34.8% (non-CKD) *vs.* 50.8% (CKD); P=0.041] and higher plaque disruption [5.5% (non-CKD) *vs.* 13.1% (CKD); P=0.049] (96). Ogita *et al.* established that in a study of stable angina patients, diabetics with CKD, had a greater proportion of dense calcium (8.9% *vs.* 6.2%; P<0.05) and necrotic core compared to non-diabetics, with a progressive increase in necrotic core associated with declining renal function; in particular the highest values were seen in RRT patients (97). Kono *et al.* evaluated both stable angina and ACS patients and clearly demonstrated on IVUS that as GFR reduced there was a significantly increased volume of dense calcification and necrotic core with the highest values in ACS patients on RRT (98). Interestingly, a meta-analysis of 989 patients from plaque progression studies stratified patients by GFR >60 and <60 (including RRT patients) and concluded that there was no difference in progression rates of atheroma volume despite preventive therapies (84).

Obesity

The worldwide prevalence of obesity is reaching pandemic status and there are strong links between obesity and CAD, which makes imaging of these patients all the more relevant. There is compelling evidence to support an association between obesity and CACS as was seen in over 6,000 patients analysed in the MESA study (99). Furthermore, in a cross-sectional study of 14,828 metabolically healthy adults without CAD, individuals with a higher BMI had a greater CACS prevalence compared to their normal weight counterparts (odds ratio 2.26; 95% CI: 1.48 to 3.43) (100). The question of progression of plaque burden in obese patients was evaluated by Cassidy *et al.* in a study

that reviewed baseline CACS and follow up at a median of 8.9 years. This demonstrated that waist circumference (P=0.024); waist-to-hip ratio (P<0.001) and BMI (P=0.036) were all strongly associated with an increased progression of CACS in those initially deemed to be of low risk (101). Additionally, Imai *et al*. studied 553 patients who underwent serial CT coronary angiography and noted that the risk of non-calcified plaques increased as visceral adipose tissue increased, with the highest quartile conferring the greatest risk (quartile IV odds ratio 4.7; 95% CI: 2.3–9.4, P value <0.001), regardless of underlying CAD risk factors.

Few invasive studies have been performed with the specific aim of evaluation of obesity and coronary plaque with most studies utilising IVUS to assess the effects of pharmacologic therapy on plaque progression. A large systematic review of seven serial IVUS studies comprising 3,459 patients to monitor atheroma progression in patients with the metabolic syndrome demonstrated that a BMI ≥30 independently predicted plaque progression (odds ratio 1.18, 95% CI: 1.00–1.40; P=0.05) (42).

Plaque vulnerability and its association with obesity have also been reviewed by multi-modality assessment. Ohashi *et al*. showed that visceral adiposity independently predicted the presence (odds ratio 1.68; 95% CI: 1.28 to 2.22) and extent (odds ratio 1.31; 95% CI: 1.03 to 1.68) of noncalcified coronary plaque that also contained multiple features of plaque vulnerability (positive remodelling, spotty calcification and low attenuation plaque)—however BMI itself was not found to be a significant predictor (102). Similarly, another prospectively performed CTCA study demonstrated that visceral abdominal fat predicted the progression of noncalcified but not calcified plaque after a mean of 38 months follow-up independent of other risk factors (103). In a large retrospective database of 3,158 patients to evaluate plaque characteristics, 32% of patients with BMI >25 kg/m^2 demonstrated evidence of high-risk plaque features and BMI itself was an independent predictor of future ACS events (104).

Regarding invasive methods to assess plaque vulnerability, Kang *et al*. reviewed 780 patients undergoing PCI with IVUS. It was noted that increasing BMI was associated with a greater plaque burden and plaque area compared to lower BMI controls (105). Tani *et al*. demonstrated that increasing BMI attenuated statin induced atherosclerotic regression and BMI was well correlated with precent plaque volume (r=0.37, P<0.001) and an independent predictor of plaque volume change (beta coefficient 0.326, 95% CI 0.003 to 0.037; P<0.05) (106). Finally Yonetsu *et al*. studied patients undergoing 3-vessel OCT in patients with and without diabetes and the metabolic syndrome. Those with the metabolic syndrome had higher BMIs and longer lipid plaque length and index compared to control patients (28).

Obesity is not only linked with increased atherosclerotic plaque burden and progression, but is also associated with attenuated response to therapies, increased plaque vulnerability and events. Its association with metabolic syndrome and DM further complicates the management of obesity.

Conclusions

Intravascular imaging techniques give unparalleled information about atherosclerotic plaques and CTCA allows assessment of plaque extent and morphology non-invasively. These imaging techniques allows us to appreciate *in vivo*, the various stages of plaque development, determine plaque burden, identify high risk plaque features, monitor response to therapy and appreciate the differences in disease pattern in various "at risk" groups. Understanding the differences in phenotype and response to therapy in various susceptible groups is vital in our endeavours to develop personalised medicine.

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Footnote

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